JC08 Rec'd PCT/PTO 30 JAN 2001

SUBSTITUTE FORM PTO-1390 U S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER
00537-182002

U.S. APPLICATION NO. (If Known, see 37 CFR 1.5) 09/744846

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US99/17294	29 July 1999	30 July 1998

TITLE OF INVENTION
METHODS OF USING A SOMATOSTATIN ANALOGUE

APPLICANT(S) FOR DO/EO/US
Jacques-Pierre Moreau

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f)).
4. ☒ The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is attached hereto (required only if not communicated by the International Bureau).
   b. ☐ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 16 below concern other documents or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

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CERTIFICATE OF MAILING BY EXPRESS MAIL Express Mail Label No EL266436255US

I hereby certify under 37 CFR §1 10 that this correspondence is being deposited with the United States Postal Service as Express Mail Post Office to Addressee with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D C. 20231

Jan. 30, 2001 Samantha Bell Samantha Bell

Date of Deposit Signature Typed Name of Person Signing

JC09 Rec'd PCT/PTO 30 JAN 2001

U.S. APPLICATION NO. (IF KNOWN) 09/744846	INTERNATIONAL APPLICATION NO. PCT/US99/17294	ATTORNEY'S DOCKET NUMBER 00537-182002

17. ☒ The following fees are submitted:

Basic National Fee (37 CFR 1.492(a)(1)- (5)):

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO..... **$710**

International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4)..... **$690**

International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4)..... **$100**

	CALCULATIONS PTO USE ONLY	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$860.00	
Surcharge of **$130** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$0.00	

Claims	Number Filed	Number Extra	Rate		
Total Claims	5 - 20 =		x **$18**	$0.00	
Independent Claims	2 - 3 =		x **$80**	$0.00	
MULTIPLE DEPENDENT CLAIMS(S) (if applicable)			+ **$270**	$0.00	
TOTAL OF ABOVE CALCULATIONS =				$0.00	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				$0.00	
SUBTOTAL =				$0.00	
Processing fee of **$130** for furnishing the English Translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f))				$0.00	
TOTAL NATIONAL FEE =				$0.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$0.00	
TOTAL FEES ENCLOSED =				$860.00	
				Amount to be refunded:	$
				Charged:	$

a. ☒ A check in the amount of $860.00 to cover the above fees is enclosed.
b. ☐ Please charge my Deposit Account No. 06-1050 in the amount of $0.00 to cover the above fees. A duplicate copy of this sheet is enclosed.
c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-1050. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b) must be filed and granted to restore the application to pending status.

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REGISTRATION NUMBER 34,053

09/744846
PCT/US99/17294

JC02 Rec'd PCT/PTO 30 JAN 2001

METHODS OF USING A SOMATOSTATIN ANALOGUE

Background of the Invention

The present invention is directed to a method of treating one or more of the following diseases and/or conditions in a patient in need thereof, which comprises the administration of the compound of the formula H-β-D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2 (also known as lanreotide), where the two Cysteines are bonded by a disulfide bond, or a pharmaceutically acceptable salt thereof, most preferably the acetate salt of the compound, in the treatment of certain diseases and/or conditions such as gastroenterological conditions and/or diseases, such as Crohn's disease, systemic sclerosis, external and internal pancreatic pseudocysts and ascites, VIPoma, nesidoblastosis, hyperinsulinism, gastrinoma, Zollinger-Ellison Syndrome, diarrhea, AIDS related diarrhea, chemotherapy related diarrhea, scleroderma, Irritable Bowel Syndrome, pancreatitis, upper gastrointestinal bleeding, postprandial portal venous hypertension especially in cirrhotic patients, complications of portal hypertension, small bowel obstruction, gastroesophageal reflux, duodenogastric reflux and in treating endocrinological diseases and/or conditions, such as Cushing's Syndrome, gonadotropinoma, hyperparathyroidism, Graves' Disease, diabetic neuropathy, macular degeneration, hypercalcemia of malignancy, Paget's disease, and polycystic ovary disease; in treating various types of cancer such as thyroid cancer, leukemia, meningioma and conditions associated with cancer such as cancer cachexia; in the treatment of such conditions as hypotension such as orthostatic hypotension and postprandial hypotension and panic attacks.

Lanreotide is an analog of somatostatin and is known to inhibit growth hormone release as well as inhibit insulin, glucagon and pancreatic exocrine secretion.

U.S. Patent No. 4,853,371 discloses lanreotide, a method for making it and a method for inhibiting the secretion of growth hormone, insulin, glucagon and pancreatic exocrine secretion.

U.S. Patent No. 5,147,856 discloses the use of lanreotide of treating restenosis.

U.S. Patent No. 5,411,943 discloses the use of lanreotide for treating hepatoma.

U.S. Patent No. 5,073,541 discloses the use of lanreotide for treating lung cancer.

U.S. Application No. 08/089,410 filed July 9, 1993 discloses the use of lanreotide for treating melanoma.

U.S. Patent No. 5,504,069 discloses the use of lanreotide for inhibiting the accelerated growth of a solid tumor.

U.S. Application No. 08/854,941 filed May 13, 1997, discloses the use of lanreotide for decreasing body weight.

U.S. Application No. 08/854,943 filed May 13, 1997, discloses the use of lanreotide for treating insulin resistance and Syndrome X.

U.S. Patent No. 5,688,418 discloses the use of lanreotide for prolonging the survival of pancreatic cells.

PCT Application No. PCT/US97/14154 discloses the use of lanreotide for treating fibrosis.

U.S. Application No. 08/855,311 filed May 13, 1997, discloses the use of lanreotide for treating hyperlipidemia.

U.S. Application No. 08/440,061 filed May 12, 1995, discloses the use of lanreotide for treating hyperamylinemia.

U.S. Application No. 08/852,221 filed May 7, 1997, discloses the use of lanreotide for treating hyperprolactinemia and prolactinomas.

The contents of the foregoing patents and applications are incorporated herein by reference.

Summary of the Invention

This invention is directed to a method of treating a disease or condition which comprises administering to a patient in need thereof an effective amount of the compound H-β-D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2, where the two Cysteines are bonded by a disulfide bond, or a pharmaceutically acceptable salt thereof, wherein the disease or condition is selected from the group consisting of systemic sclerosis, pancreatic pseudocysts, pancreatic ascites, VIPoma, nesidoblastosis, hyperinsulinism, gastrinoma, Zollinger-Ellison Syndrome, hypersecretory diarrhea, scleroderma, irritable bowel syndrome, upper gastrointestinal bleeding, postprandial portal venous hypertension, complications of portal hypertension, small bowel obstruction, duodenogastric reflux, Cushing's

Syndrome, gonadotropinoma, hyperparathyroidism, diabetic neuropathy, macular degeneration, hypercalcemia of malignancy, Paget's disease, meningioma, cancer cachexia, psoriasis, hypotension and panic attacks.

A preferred method of the immediately foregoing method is where the acetate salt of H-β-D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2 is administered.

A preferred method of the immediately foregoing method is where the disease or condition is selected from the group consisting of VIPoma, nesidoblastosis, hyperinsulinism, gastrinoma, hypersecretory diarrhea, irritable bowel syndrome, upper gastrointestinal bleeding, postprandial portal venous hypertension, especially in cirrhotic patients, complications of portal hypertension, small bowel obstruction, diabetic neuropathy, meningioma and cancer cachexia.

A preferred method of the immediately foregoing method is where the disease or condition treated is selected from the group consisting of VIPoma, nesidoblastosis, hypersecretory diarrhea, irritable bowel syndrome, small bowel obstruction and diabetic neuropathy.

In another aspect, the present invention is directed to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of the acetate salt of H-β-D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2 to treat a disease or condition wherein the disease or condition is selected from the group consisting of systemic sclerosis, pancreatic pseudocysts, pancreatic ascites, VIPoma, nesidoblastosis, hyperinsulinism, gastrinoma, Zollinger-Ellison Syndrome, hypersecretory diarrhea, scleroderma, irritable bowel syndrome, upper gastrointestinal bleeding, postprandial portal venous hypertension, especially in cirrhotic patients, complications of portal hypertension, small bowel obstruction, duodenogastric reflux, Cushing's Syndrome, gonadotropinoma, hyperparathyroidism, diabetic neuropathy, macular degeneration, hypercalcemia of malignancy, Paget's disease, meningioma, cancer cachexia, psoriasis, hypotension and panic attacks.

Detailed Description

Lanreotide is readily prepared according to the procedure disclosed in U.S. Patent No. 4,853,371, or the procedure disclosed in U.S. Patent No. 5,411,943, the teachings of which are incorporated herein by reference.

Lanreotide is currently marketed as the acetate salt in a 30 mg long-acting form and is available from Ipsen Biotech, Paris, France.

As is well known to those skilled in the art, the known and potential uses of somatostatin are varied and multitudinous. Somatostatin is known to be useful in the treatment of the diseases and/or conditions listed hereinbelow. The varied uses of somatostatin may be summarized as follows: Cushings Syndrome (see Clark, R.V. et al, Clin. Res. 38, p. 943A, 1990); gonadotropinoma (see Ambrosi B., et al., Acta Endocr. (Copenh.) 122, 569-576, 1990); hyperparathyroidism (see Miller, D., et al., Canad. Med. Ass. J., Vol. 145, pp. 227-228, 1991); Paget's disease (see, Palmieri, G.M.A., et al., J. of Bone and Mineral Research, 7, (Suppl. 1), p. S240 (Abs. 591), 1992); VIPoma (see Koberstein, B., et al., Z. Gastroenterology, 28, 295-301, 1990 and Christensen, C., Acta Chir. Scand. 155, 541-543, 1989); nesidioblastosis and hyperinsulinism (see Laron, Z., Israel J. Med. Sci., 26, No. 1, 1-2, 1990, Wilson, D.C., Irish J. Med. Sci., 158, No. 1, 31-32, 1989 and Micic, D., et al., Digestion, 16, Suppl. 1.70. Abs. 193, 1990); gastrinoma (see Bauer, F.E., et al., Europ. J. Pharmacol., 183, 55 1990); Zollinger-Ellison Syndrome (see Mozell, E., et al., Surg. Gynec. Obstet., 170, 476-484, 1990); hypersecretory diarrhea related to AIDS and other conditions (due to AIDS, see Cello, J.P., et al., Gastroenterology, 98, No. 5, Part 2, Suppl., A163 1990; due to elevated gastrin-releasing peptide, see Alhindawi, R., et al., Can. J. Surg., 33, 139-142, 1990; secondary to intestinal graft vs. host disease, see Bianco J.A., et al., Transplantation, 49, 1194-1195, 1990; diarrhea associated with chemotherapy, see Petrelli, N., et al., Proc. Amer. Soc. Clin. Oncol., Vol. 10, P 138, Abstr. No. 417 1991); irritable bowel syndrome (see O'Donnell, L.J.D., et al., Aliment. Pharmacol. Therap., Vol. 4., 177-181, 1990); pancreatitis (see Tulassay, Z., et al., Gastroenterology, 98, No. 5, Part 2, Suppl., A238, 1990); Crohn's Disease (see Fedorak, R.N., et al., Can. J. Gastroenterology, 3, No. 2, 53-57, 1989); systemic sclerosis (see Soudah, H., et al., Gastroenterology, 98, No. 5, Part 2, Suppl., A129, 1990); thyroid cancer (see Modigliani, E., et al., Ann., Endocr. (Paris), 50, 483-488, 1989); psoriasis (see Camisa, C., et al., Cleveland Clinic J. Med., 57 ,No. 1, 71-76, 1990); hypotension (see Hoeldtke, R.D., et al., Arch. Phys. Med. Rehabil., 69, 895-898, 1988 and Kooner, J.S., et al., Brit. J. Clin. Pharmacol., 28, 735P-736P, 1989); panic attacks (see Abelson, J.L., et al., Clin. Psychopharmacol., 10, 128-132, 1990); sclerodoma (see Soudah, H., et al., Clin. Res., Vol. 39, p. 303A, 1991);

small bowel obstruction (see Nott, D.M., et al., Brit. J. Surg., Vol. 77, p. A691, 1990); gastroesophageal reflux (see Branch, M.S., et al., Gastroenterology, Vol. 100, No. 5, Part 2 Suppl., p. A425, 1991); duodenogastric reflux (see Hasler, W., et al., Gastroenterology, Vol. 100, No. 5, Part 2, Suppl., p. A448, 1991); Graves' Disease (see Chang, T.C., et al., Brit. Med. J., 304, p. 158, 1992); polycystic ovary disease (see Prelevic, G.M., et al., Metabolism Clinical and Experimental, 41, Suppl. 2, pp 76-79, 1992); upper gastrointestinal bleeding (see Jenkins, S.A., et al., Gut., 33, pp. 404-407, 1992 and Arrigoni, A., et al., American Journal of Gastroenterology, 87, p. 1311, (abs. 275), 1992); pancreatic pseudocysts and ascites (see Hartley, J.E., et al., J. Roy. Soc. Med., 85, pp. 107-108, 1992); leukemia (see Santini, et al., 78, (Suppl. 1), p. 429A (Abs. 1708), 1991); meningioma (see Koper, J.W., et al., J. Clin. Endocr. Metab., 74, pp. 543-547, 1992); and cancer cachexia (see Bartlett, D.L., et al., Surg. Forum., 42, pp. 14-16, 1991). The contents of the foregoing references are incorporated herein by reference.

Surprisingly, the Applicant has now discovered that lanreotide itself was particularly useful in treating the conditions, disorders and disease noted hereinabove.

The usefulness of lanreotide in the various disclosed new medical uses can be better understood through the results of tests relating to the treatment of upper gastrointestinal bleeding.

Lanreotide or a pharmaceutically-acceptable salt thereof can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual or topical routes of administration and can be formulated with pharmaceutically acceptable carriers to provide dosage forms appropriate for each route of administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than such inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as coca butter or a suppository wax.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. Generally, dosage levels of between 25 ?g/kg/day to 100 mg/kg/day of body weight daily are administered as a single dose or divided into multiple doses to humans and other animals, e.g., mammals, to obtain the desired therapeutic effect.

A preferred general dosage range is 250 ?g/kg/day to 5.0 mg/kg/day of body weight daily which can be administered as a single dose or divided into multiple doses.

Further, Lanreotide can be administered in a sustained release composition such as those described in the following patents. Among those formulations, 14-day or 28-day slow release formulations will be preferred. U.S.

Patent No. 5,672,659 teaches sustained release compositions comprising Lanreotide and a polyester. U.S. Patent No. 5,595,760 teaches sustained release compositions comprising Lanreotide in a gelable form. U.S. Application No. 08/929,363 filed September 9, 1997, teaches polymeric sustained release compositions comprising Lanreotide and chitosan. U.S. Application No. 08/740,778 filed November 1, 1996, teaches sustained release compositions comprising Lanreotide and cyclodextrin. U.S. Application No. 09/015,394 filed January 29, 1998, teaches absorbable sustained release compositions of Lanreotide. The contents of the foregoing patents and applications are incorporated herein by reference.

The use of immediate or of sustained release compositions depends on the type of indications aimed at. If the indication consists of an acute or over-acute disorder, a treatment with an immediate form will be preferred over the same with a prolonged release composition. On the contrary, for preventive or long-term treatments, a prolonged release composition will generally be preferred.

Typically, to the indication upper gastrointestinal bleeding will correspond an acute or over-acute treatment with a dosage of 80 to 120 ?g/day per person during approximately 5 days. After endoscopical treatment, preventive treatment against recurrence can be performed using lanreotide sustained release forms as an adjuvant to usual treatments; for this type of treatment, 14-day sustained release forms with a total dosage of approximately 30 mg lanreotide or 28-day lanreotide forms can be used.

For other indications than upper gastrointestinal bleeding, which correspond rather long term treatments, 14-day sustained release forms with a total dosage of approximately 30 mg lanreotide or 28-day lanreotide forms will be adequate.

Claims

1. A method of treating a disease or condition which comprises administering to a patient in need thereof an effective amount of the compound H-β-D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2, where the two Cysteines are bonded by a disulfide bond, or a pharmaceutically acceptable salt thereof, wherein the disease or condition is selected from the group consisting of systemic sclerosis, pancreatic pseudocysts, pancreatic ascites, VIPoma, nesidoblastosis, hyperinsulinism, gastrinoma, Zollinger-Ellison Syndrome, hypersecretory diarrhea, scleroderma, irritable bowel syndrome, upper gastrointestinal bleeding, postprandial portal venous hypertension, complications of portal hypertension, small bowel obstruction, duodenogastric reflux, Cushing's Syndrome, gonadotropinoma, hyperparathyroidism, diabetic neuropathy, macular degeneration, hypercalcemia of malignancy, Paget's disease, meningioma, cancer cachexia, psoriasis, hypotension and panic attacks.

2. A method according to claim 1 wherein the acetate salt of H-β-D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2 is administered.

3. A method according to claim 2 wherein the disease or condition is selected from the group consisting of VIPoma, nesidoblastosis, hyperinsulinism, gastrinoma, hypersecretory diarrhea, irritable bowel syndrome, upper gastrointestinal bleeding, postprandial portal venous hypertension, especially in cirrhotic patients, complications of portal hypertension, small bowel obstruction, diabetic neuropathy, meningioma and cancer cachexia.

4. A method according to claim 3 wherein the disease or condition treated is selected from the group consisting of VIPoma, nesidoblastosis, hypersecretory diarrhea, irritable bowel syndrome, small bowel obstruction and diabetic neuropathy.

5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of the acetate salt of H-β-D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2 to treat a disease or condition wherein the disease or condition is selected from the group consisting of systemic sclerosis, pancreatic pseudocysts, pancreatic ascites, VIPoma, nesidoblastosis, hyperinsulinism, gastrinoma, Zollinger-Ellison Syndrome, hypersecretory diarrhea, scleroderma, irritable bowel syndrome, upper gastrointestinal bleeding, postprandial portal venous hypertension, especially in cirrhotic patients, complications of portal hypertension, small bowel obstruction, duodenogastric

reflux, Cushing's Syndrome, gonadotropinoma, hyperparathyroidism, diabetic neuropathy, macular degeneration, hypercalcemia of malignancy, Paget's disease, meningioma, cancer cachexia, psoriasis, hypotension and panic attacks.

Attorney's Docket No.: 00537-182002
Client's Ref. No.: BPC075 US PCT US

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled METHODS OF USING A SOMATOSTATIN ANALOGUE, the specification of which:

[] is attached hereto.
[X] was filed on January 30, 2001 as Application Serial No. 09/744,846 and was amended on _____.
[X] was described and claimed in PCT International Application No. PCT/US99/17294 filed on July 29, 1999 and as amended under PCT Article 19 on _____.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information I know to be material to patentability in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim the benefit under Title 35, United States Code, §119(e)(1) of any United States provisional application(s) listed below:

U.S. Serial No.	Filing Date	Status
60/094,693	July 30, 1998	Expired

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose all information I know to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56(a) which became available between the filing date of the prior application and the national or PCT international filing date of this application:

U.S. Serial No.	Filing Date	Status
09/126,525	July 30, 1998	Abandoned

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

Country	Application No.	Filing Date	Priority Claimed
			[] Yes [] No
			[] Yes [] No

Combined Declaration and Power of Attorney

I hereby appoint the following attorneys and/or agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Y. Rocky Tsao, Reg. No. 34,053; Brian R. Morrill Reg. No. 42,098; Alan F. Feeney Reg. No. 43,609; Timothy A. French, Reg. No. 30,175; Eric L. Prahl, Reg. No. 32,590; and Frank R. Occhuiti, Reg. No. 35,306.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Full Name of Inventor: JACQUES-PIERRE MOREAU

Inventor's Signature: _____ Date: May 1st 2001

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